PUBERTY, MENSTRUATION, PREGNANCY*

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My mandate covers three critical periods in the life of woman: puberty, menstruation and pregnancy—more than four decades of her existence. Because many of the terms and concepts used in endocrinology are not clearly understood by all members of the profession, I shall give definitions of some of the terms employed.

GONADOTROPIC FACTORS stimulate both the male and female gonads. In this connection the tests used in the female animal are described. In response to gonadotropic factors the ovarian follicles and corpus luteum in the ovaries of immature animals are activated. There is a difference between the factors obtained from the prepituitary glands and those derived from pregnant mares' serum, which act upon the ovaries of hypophysectomized animals, and extracts of pregnancy urine and placenta which act mainly upon intact animals. The former (gland extracts) should be called *gonadotropic factor*, the latter (pregnancy derivatives), *chorionic gonadotropin.*

FEMALE SEX HORMONES include both estrogens and progestin. *Estrogens* are hormones mainly secreted by the ovarian follicles, corpus luteum and placenta. They produce estrus in the castrate rodent (mice, rats, rabbits, etc.).

Progestin is the special corpus luteum hormone which causes secretion and a decidual reaction in the uterine mucosa. Without these preparatory changes the fertilized ovum cannot embed.

ANDROGENS are the male sex hormones which produce comb growth in capons and immature chicks of both sexes, and restore the atrophic prostate and seminal vesicles of castrate animals. In addition to derivation from the testes, androgens have been obtained from the adrenal.

As in this series of talks no emphasis has been placed upon the intrauterine, childhood and adolescent periods, in passing I must mention that within the uterus of the mother, throughout nine months, the

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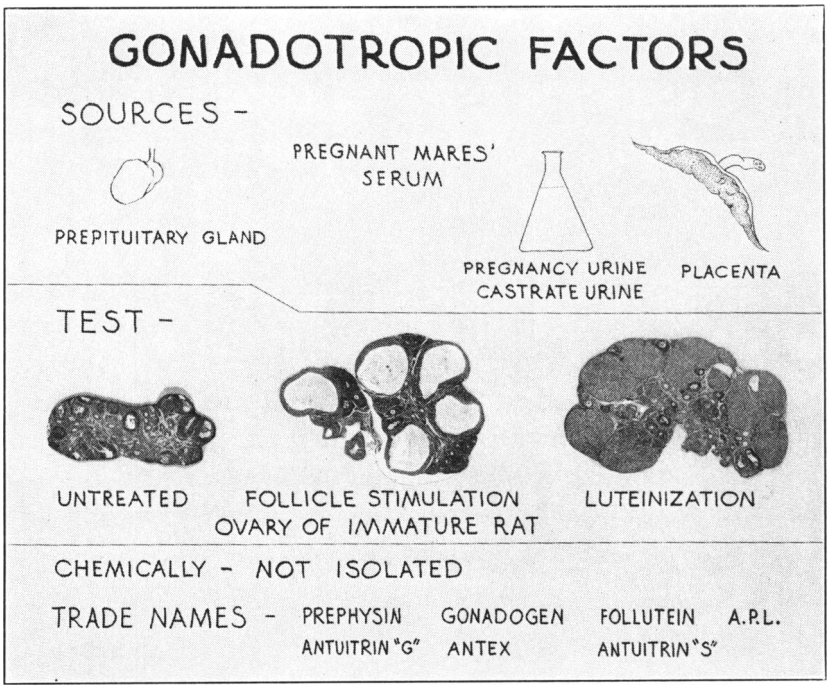

Fig. 1. Gonadotropic Factors. Gland extracts; concentrates of pregnant mares' serum; concentrates of pregnant human urine, and of placental tissue are available.

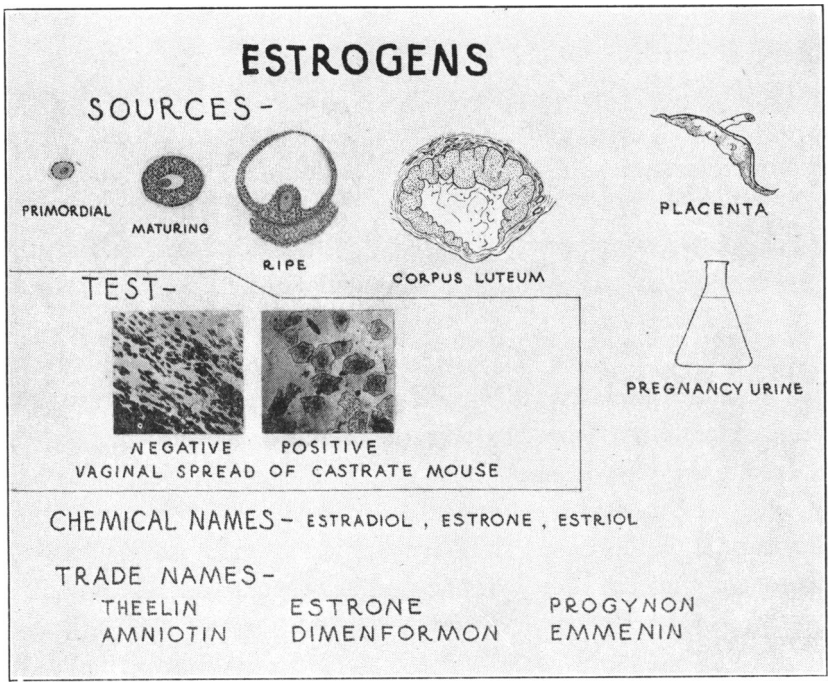

Fig. 2. Estrogens. Main source stallions' urine; other, from placenta.

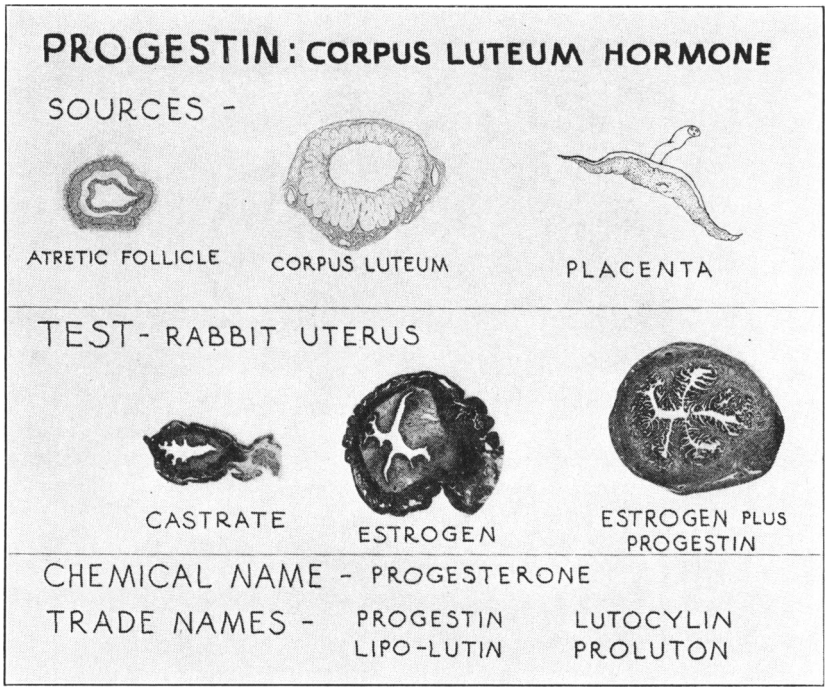

Fig. 3. Progestin. Made synthetically. Cross sections of uterus from E. Fels. *Das Hormon des Corpus Luteum.*

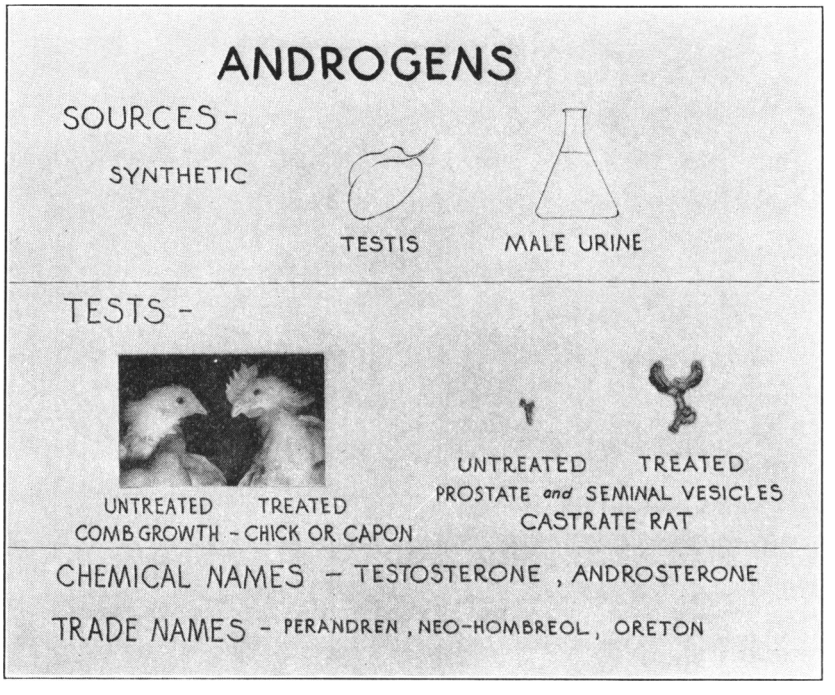

Fig. 4. Androgens. Made synthetically.

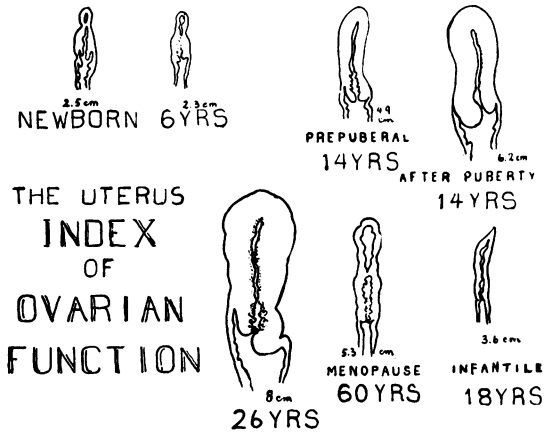

Fig. 5. Cross Sections of Human Uterus at Various Ages. Drawn to scale. Some are redrawn from H. Bayer, *Vorlesung über allgemeine Geburtshilfe.*

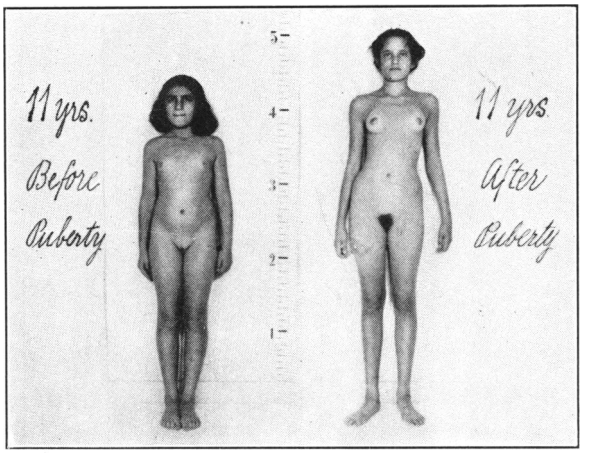

Fig. 6. Puberty Changes. At left, girl before puberty; at right, another girl of same age who menstruates.

sex organs of the fetus are stimulated by maternal and placental hormones, reaching them through the placental circulation. Therefore, at birth the uterus and breasts by their comparatively large size show anatomically the effects of this hormonal stimulation—the well known symptoms of activation, popularly known as pseudomenstruation and witch's milk. In the ensuing years the tubular organs of the female infant are smaller than at birth, but gradually by the time that the fifth year is reached, a slowly progressive increase in size of the ovaries and

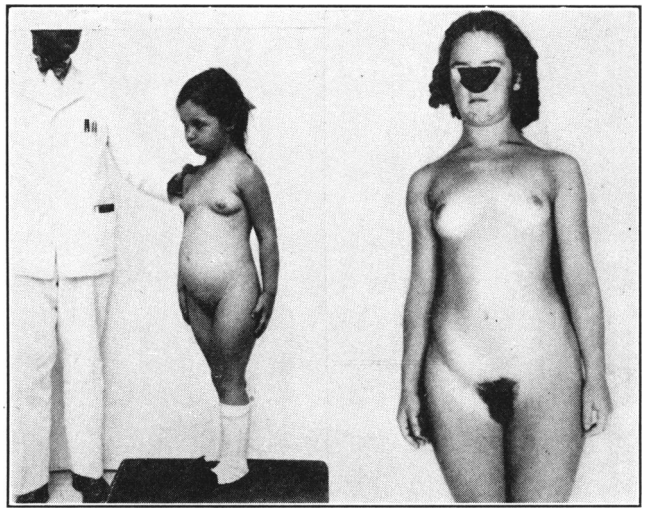

Fig. 7. PUBERTAS PRECOX. At left, child of 3 years who menstruates since age of 6 months. At right, same child at 11 years now a normal adolescent.

uterus can be noted. In the infant and adolescent, small quantities of female sex hormone, as well as male sex hormone, are excreted in the urine. In a girl, accidentally investigated three months before the onset of her menstruation, a definite sex cycle in the urine could be demonstrated.

PUBERTY

Puberty is not an instantaneous, but a slow, progressive process. Clinically it manifests itself by the development of pubic and axillary hair, increase in size of the breasts, changes in the fat distribution, which becomes more markedly feminine, slowing or arrest of growth, and a very definite psychical and emotional transformation toward the feminine. The most obvious evidence of the full development of normal puberty is the onset of menstruation. However, absence of menstruation, that is true primary amenorrhea, may mask the exact determination of the time of puberty.

The hormonal forces which produce puberty have been discussed by previous speakers. Nevertheless, no convincing explanation, for the onset of cyclical pituitary function which initiates the ovarian stimulus has as yet been adduced. The activated ovary produces the follicular and luteinizing phases in the uterus and the complete cycle terminates in menstruation.

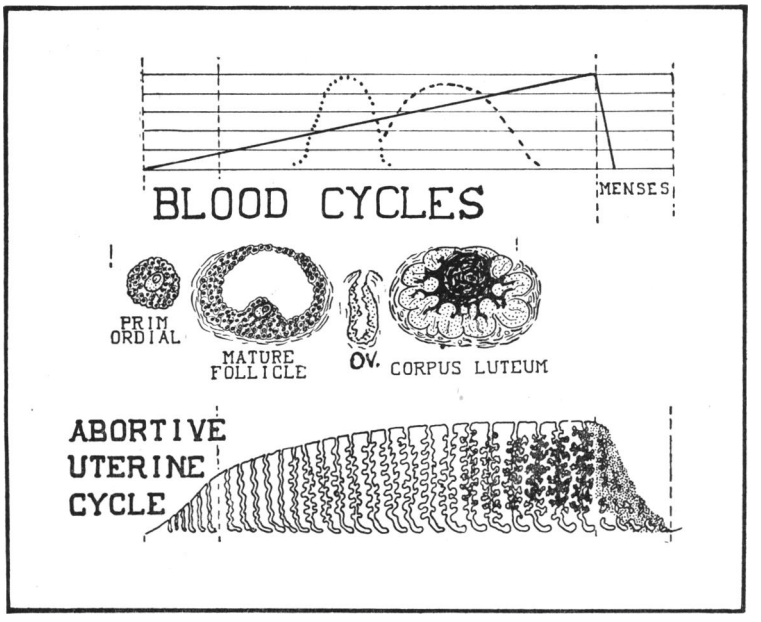

Fig. 8. Diagram of Blood, Ovarian and Uterine Menstrual Cycles. *Above: Blood Cycle:* Solid line, estrogens; dotted line, prepituitary; broken line, progestin. *Middle:* Follicle, ovulation (Ov.), corpus luteum. *Below:* Uterine mucosa.

Puberty is largely dependent upon normal infantile and preadolescent development. However, the menarche may occur in very badly handicapped individuals, and fail to appear in adolescents who show few or no recognizable endocrine disturbances. The most common and most easily diagnosed as well as remediable postponements of puberty are due to hypothyroidism, obesity or severe malnutrition. It is my firm conviction that many of the disabilities noted in the female genital tract in adults might have been avoided if we had had the opportunity of recognizing these disturbances during adolescence and the ability to remedy them at this stage.

The time of onset of puberty and menstruation varies greatly, influenced by individual, familial, ethnic and climatic factors. Premature sexual maturity (noted as early as three months) may be due to unknown causes (so-called essential), or to tumors of the ovary, pineal or adrenal glands.

Menstruation

Menstruation marks the stage of maturity in the female. The men-

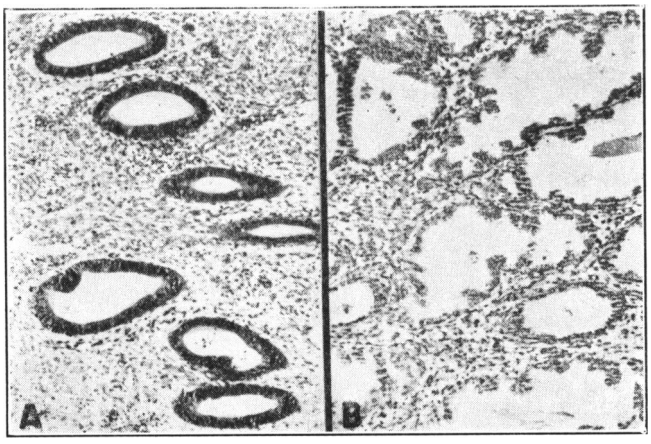

Fig. 9. Low Power Photomicrograms of Uterine Mucosa. A. Proliferative stage. B. Secretory stage.

strual cycle should begin with the onset of puberty, persist throughout the time of sexual life, and gradually fade with the approach of the menopause. The sole physiological interruptions of the menstrual cycle are caused by pregnancy and lactation.

In the normal adult female—

1. Periodic increased gonadotropic action of the anterior pituitary activates the ovaries, which respond with

2. Follicle growth, maturation of the follicle and ovulation.

3. The ovarian follicles produce *estrogen* and, after ovulation, the empty follicle sac forms the corpus luteum. This in turn secretes *progesterone* in addition to estrogen.

These two hormones (estrogens from the first to the thirteenth day; estrogen and progesterone from the thirteenth to twenty-third day) by means of the blood stream reach the uterus, tubes, vagina and breasts which are the end organs upon which these secretions act.

The biologic purpose of the uterine changes which ensue has for its sole object the preparation of a nest for a fertilized ovum. The changes in the endometrium are divisible into the estrogenic (follicular) and progestational (corpus luteum) phases, both characterized by distinctive and, if well marked, readily recognizable histologic pictures, respectively, proliferation and secretion.

If fertilization does not occur, the ovarian stimuli cease, involutional intrauterine changes abruptly supervene, culminating in the endometrial

desquamation or transmucosal bleeding which we term menstruation. Physiologically menstruation in the human may be regarded as a pseudo-abortion.

These monthly processes have been thoroughly studied from many angles, including the morphologic changes which have been observed in the hypophysis; the full sequence of growth of the primordial follicle to the Graafian stage; its rupture and corpus luteum formation in the ovary; the hormonal cycles (gonadotropic, estrogenic, proluteinic) in the blood and urine; and the consequent changes appearing in the end organs.

Variations in the twenty-eight day menstrual cycle are frequent. They commonly take either the form of diminution, retardation or omission of menstruation, or their *clinical* antithesis, namely, increased amount, prolongation or too frequent flow.

Amenorrhea, however, may occur in the presence of apparently adequate hormonal blood cycles.

Menorrhagia and metrorrhagia most frequently are due to overfunction of follicular ovarian action. Some but as yet indecisive evidence has been offered that particular types of excess bleeding are due to quantitative disturbance between follicular and lutein phases. I shall again refer to this subject.

Pregnancy

Somewhere in the lifetime of a female, impregnation may occur; this happens most often around the eleventh to fourteenth day of the cycle. If then the fertilized ovum reaches the progestational endometrium, it should embed and grow there. From the very onset of nidation, a tremendous change in the hormonal balance ensues. The anterior pituitary-like hormone found in the blood and in the urine increases a thousand-fold over that found in the non-pregnant. Upon this change are based the pregnancy tests (Aschheim-Zondek; Friedman). The amount of estrogen progressively increases both in the blood and in the excretions, from the second month onward. A steadily progressive increase in the urinary progesterone has likewise been noted until the fifth month.

Such tremendous acceleration of hormonal stimuli manifests itself by striking general changes: increase in size of the uterus, development of the breasts, increased vascularization of the genital sphere, and the speeding up of many endocrine functions (pituitary, adrenal, thyroid). The

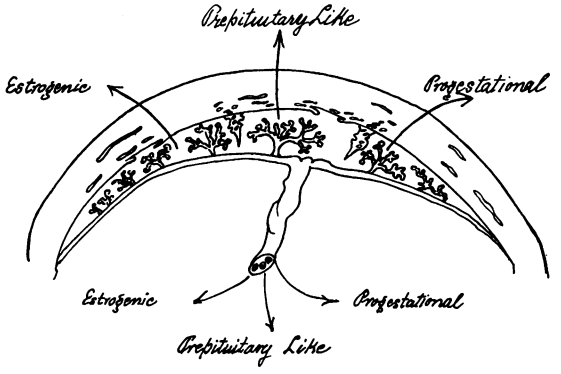

Fig. 10. DIAGRAM OF PLACENTAL SECRETION. "THE GESTATIONAL GLAND." *Upward* pointing arrows show secretion into maternal circulation, *downward,* into fetal blood stream.

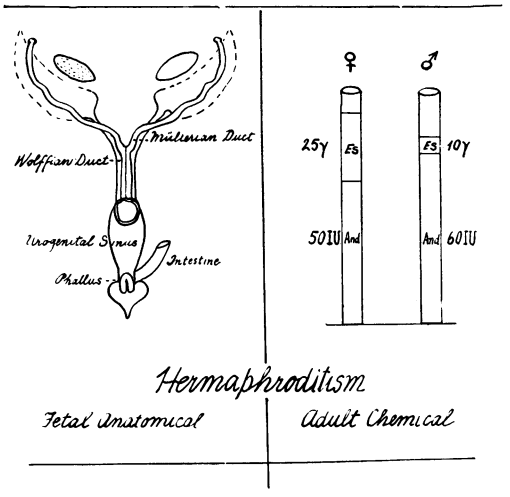

Fig. 11. DIAGRAM OF "NORMAL HUMAN HERMAPHRODITISM. *Left.* Early fetal bisexual development of Wolffian and Müllerian ducts. *Right.* Chemical adult hermaphroditism. Presence of estrogens and androgens in blood and excretion of both sexes.

placenta develops into a temporary gland of internal secretion (the Gestational Gland) which produces locally anterior pituitary-like (chorionic gonadotropin), estrogenic and progestational hormones, affording to the uterus and its contained fetus an almost autonomous supply of sex hormones.

In spite of much investigation, a hormonal causation of labor has not as yet been firmly established. With the expulsion of the fetus and placenta, a rapid return to the pregravid status, in fact a slump below the

normal production of hormones, takes place, causing hyperinvolutionary changes when exaggerated or prolonged.

Ratio of Femaleness to Maleness

Recently an additional factor has had to be considered. After the discovery of an adult chemical hermaphroditism in both sexes, which shows itself by the presence in the female of male sex hormone and in the male of female sex hormone, the ratio between maleness and femaleness in a given individual has assumed importance. Which of the malfunctions or functional diseases can be ascribed to severe disturbances of this ratio, femaleness to maleness, is still a moot question which is being investigated in numerous research laboratories. A striking example is observed in the female in the adrenocortical syndrome.

Functional Disturbances

The foregoing briefly and in bare outline covers the essentials, as far as known, of the complicated hormonal processes which produce puberty and control menstruation, as well as pregnancy. Deviations ascribable to hormonal changes are known as functional diseases. Of these functional disturbances, I instance a few clearcut clinical entities, though I must warn you that, upon analysis, their hormonal basis is still little understood. In the first group fall mainly the amenorrheas, both primary and secondary, sterility and dysmenorrhea; in the second, menorrhagia, metrorrhagia and premenstrual tension.

Before ascribing these symptoms to functional disturbances, it is essential that we exclude organic diseases. In the amenorrhea group, such conditions as malformations of the genitals (absent vagina) and pregnancy frequently have been overlooked. In the second group, of excessive bleeding, fibroids and neoplasms, particularly of the ovaries and of the cavity of the uterus, are the most frequent causes of error.

In order to obtain an insight concerning the hormonal conditions met with, our group has sought to devise methods of concentration for estrogens, androgens and gonadotropic factors obtained both from the blood and the urine.

Unfortunately the blood concentration of hormones normally is low and therefore only one animal may be used for each test unless unjustifiably large amounts of blood are withdrawn. Some physiologists have therefore taken exception to these results because, as is well known, the

reactivity of individual animals varies greatly. Fully aware of this variability, we have graded our blood tests considerably above the average reactivity of the animal used. For example, before menstruation, 30 cc. of normal woman's blood should contain a mouse unit of estrogen; we use 40 cc. This allows a wide margin. Fourteen years trial has convinced us of the reliability of the estrogenic and gonadotropic blood tests. If more delicate tests become available, they may alter the number of units obtained, but probably will merely change the scale without affecting their relative proportion. The urine tests are performed with larger groups of animals and the results therefore meet statistical requirements.

Our further investigations have necessitated a revision of the view, first entertained, that amenorrheas are always due to underfunction of the ovary. It appears that no single cause can be found for amenorrhea. Amenorrheic women may secrete a normal amount of estrogen, too little or even too much. The gonadotropic cycle in both blood and urine may likewise be normal, high or low.

These findings in amenorrhea are difficult to interpret, particularly as we have also found that amenorrheic women, in contrast to women in the full menopause (women even up to seventy years), *require from six to ten times larger doses of estrogen than in the menopause*, to produce a single uterine bleeding. This may signify that the uterus in amenorrhea is more refractory to estrogens.

The hormone titers obtained in functional sterility closely parallel those obtained in amenorrhea, that is, normal, under, or overfunctioning of the ovaries. Recently we have seen that amenorrheic as well as sterile women may have what is considered a normal excretion of sodium pregnandiol in the urine. If the interpretations of Venning and Browne are accepted, this would signify ovulation. I am as yet unwilling to accept the presence of sodium pregnandiol in the urine as conclusive evidence of ovulation. It must not be forgotten that in the growing and atretic follicles, the thecal tissues frequently show luteal proliferation, which may well account for a progestational excretory product. This does not signify that I agree with some clinical investigators that the anovulatory cycle is as common in the human being as has been suggested.

In menorrhagia and metrorrhagia the blood concentration of gonadotropic and estrogenic hormone may be normal; more often it is low. The urine excretion of estrogen, on the other hand, is regularly excessive, a characteristic of this group. Instead of the normal excretion of

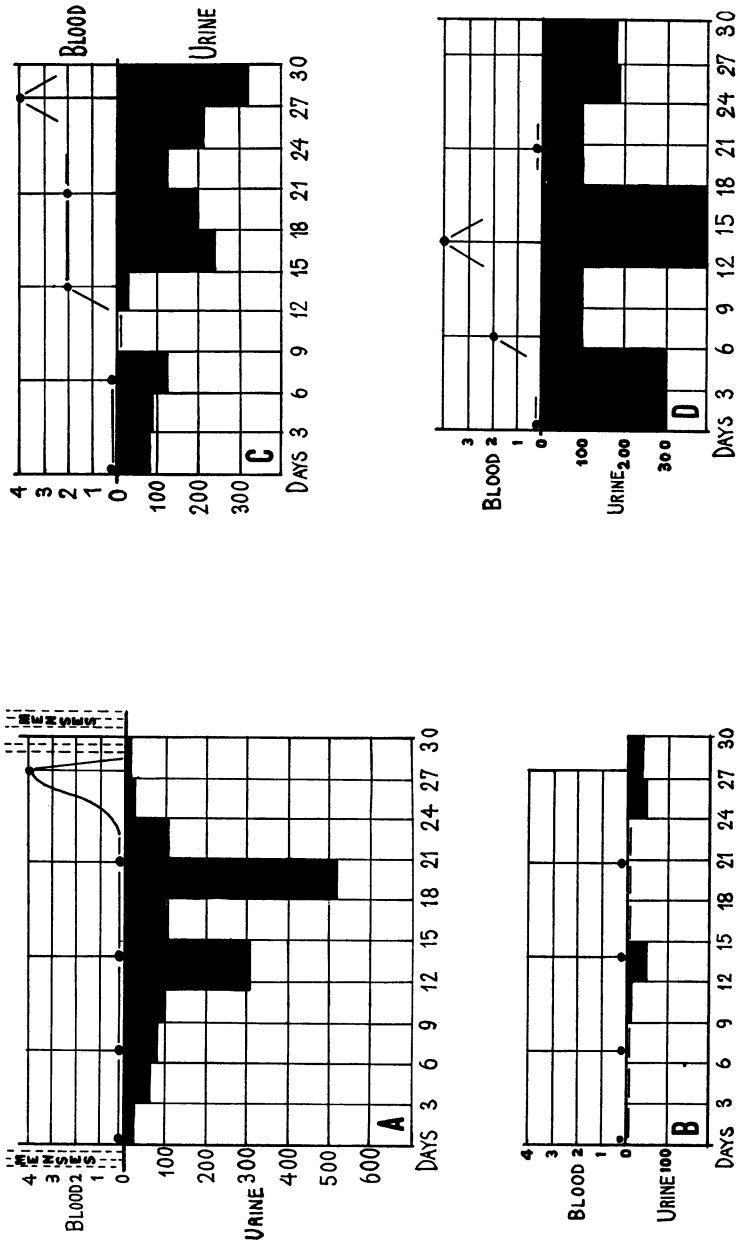

Fig. 12. Graphs of Estrogenic Blood and Urinary Cycles. A. *Normal Menstruating Female.* Premenstrual blood concentration corresponding to 25 M.U. per liter. Total excretion in urine in 30 days equals 1500 I.U. B. *Primary Amenorrhea.* Acyclical. No demonstrable blood concentration. Total excretion 135 I.U. C. *Secondary Amenorrhea.* Four years' duration. Cyclical blood concentration; normal excretion (1400 I.U.). D. *Primary Amenorrhea.* Cyclical blood concentration. Excretion somewhat above normal (2200 I.U.).

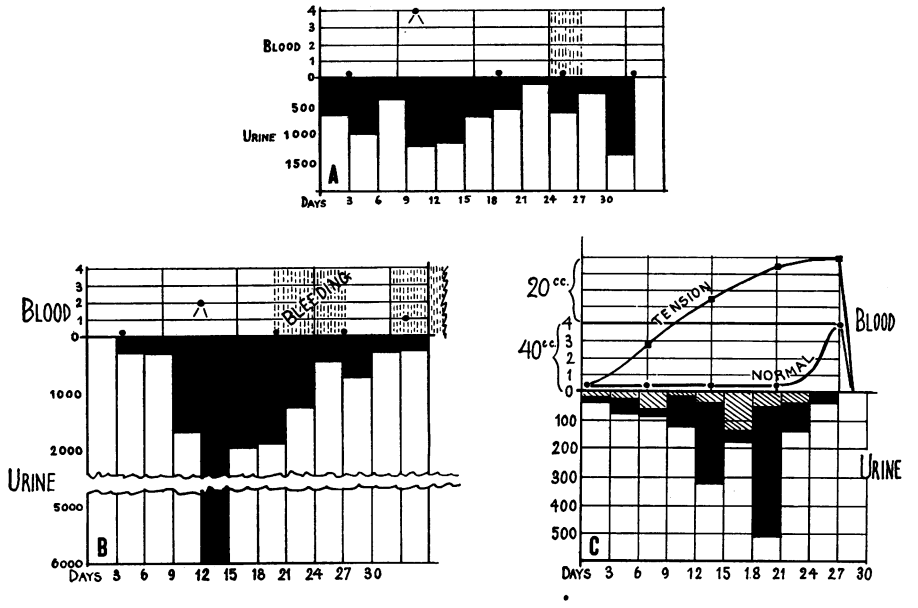

Fig. 13. Graphs of Estrogenic Blood and Urinary Cycles. A. *Menorrhagia.* Cyclical blood concentration. Excretion 7500 I.U. B. *Menorrhagia.* Subthreshold blood concentration; excessive urinary excretion (15,000 I.U.). C. *Premenstrual Tension.* Contrasting normal and "tension" premenstrual blood concentration. Urinary excretion in "tension" 400 I.U. (shaded), in contrast to normal, 1490 I.U. (solid black).

1200 to 1500 international units of estrogen, from 2500 to 15,000 units are excreted during this same period of time. These findings may be interpreted either as ovarian overproduction or failure of utilization of estrogenic hormone.

In contrast, in a group which I call "premenstrual tension," characterized by excessive neurovascular and psychic phenomena preceding menstruation, at once relieved by the appearance of the menstrual flow, different hormonal findings are observed. The blood concentration of estrogen is increased throughout the cycle. Premenstrually a positive reaction is regularly obtained with 20 cc. of blood instead of 40 cc. The urinary excretion is greatly diminished, only from 300 to 500 international units of estrogens being excreted during thirty days. According to my present interpretation, this signifies a retention of estrogens in the blood stream, with resulting autonomic symptoms.

Whether variations in kidney permeability (either too high or too low threshold) with consequent differences in blood hormone levels,

irrespective of ovarian activity, or non-utilization and failure of destruction of the estrogens play the decisive role, must remain an open question.

Therapy

To the patient, as well as to the physician, successful therapy is of vital importance. The results obtained by means of the various hormones have always given rise to the utmost diversity of opinion. The practitioner is in the unfortunate position of having to depend largely upon the reports of laboratory and clinical investigators. Animal experimentation allows of various interpretations. Clinical investigations, unless striking, as in the present treatment of the menopause, are almost impossible to evaluate critically.

Some of the effects of estrogens, such as the conversion of the thin, non-resistant vaginal epithelium of the infant into a thicker keratinized mucosa, are well authenticated and are of help in the cure of infantile and adolescent gonorrhea. The relief of menopause symptoms by means of the natural and synthetic estrogens is well established. Progesterone appears promising in the treatment of dysmenorrhea and habitual abortion, although the effects are not as clearcut. Even less assured, though still promising, is the reduction of bleeding in functional menorrhagia and metrorrhagia by means of progesterone. The treatment of excessive functional bleeding with androgens theoretically meets many requirements because its primary effect in reducing the gonadotropic excretion of the pituitary is what is sought for, and little if any stimulation of the uterus results. Androgens at times, however, have produced masculinizing symptoms such as hirsutism, coarsening of the voice and increase in size of the clitoris, only the latter appearing reversible. Therefore I counsel against the use of male hormone in the female unless possibly vital indications necessitate its employment. In my hands estrogens as well as gonadotropic prepituitary preparations have proved of no value whatever in the treatment of amenorrhea.

In spite of many glowing reports, I am unable to record any results obtained in the female with prepituitary gonadotropic factors, whether obtained from the gland or concentrates of pregnancy urine, with the possible exception of some increase in the growth of pubic hair.

I am entirely unconvinced by the evidence submitted that the available prepituitary gland preparations, whether labeled "growth" or "gon-

adotropic" have any therapeutic effect on body growth or on the female genital function. For every case reported as cured by daily injections, given over periods of twelve to thirty-six months, I can show a greater number of patients in whom two to five inches of growth has taken place unexpectedly in the course of one to three years (hypogonad; pseudo-Froehlich) and others who have menstruated for the first time, or after periods of amenorrhea of two to seven years duration, without any therapy. The intravenous injection of concentrates of pregnant mares' serum may prove more effective.

In regard to prepituitary therapy, therefore, we still are in the dark epoch comparable to that of thirty years ago when the profession, at large, dosed their patients with inert, defatted ovarian powder and reported good results which then, as now, should be credited to Mother Nature.

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